IUCLID

Data Set

Existing Chemical	:	ID: 123-18-2
Memo	:	Isobutyl Heptyl Ketone (IBHK)
CAS No.	:	123-18-2
EINECS Name	:	2,6,8-Trimethylnonan-4-one
EC No.	:	204-607-3
TSCA Name	:	4-Nonanone, 2,6,8-trimethyl-
Molecular Formula	:	C12H24O

Producer related part

Company	:	TRS Inc.
Creation date	:	12.09.2003

Substance related part

Company	:	TRS Inc.
Creation date	:	12.09.2003
Status	:	
Memo	:	
Printing date	:	02.12.2005
Revision date	:	
Date of last update	:	02.12.2005
Number of pages	:	91
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	O=C(CC(CC(C)C)C)CC(C)C
Molecular formula	:	C12 H24 O1
Molecular weight	:	184.32
Petrol class	:	

05.12.2003

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	
Colour	:	transparent colorless
Odour	:	obnoxious
Remark	:	Purity/Composition: >=95 and <=100% 2,6,8-Trimethyl-4-nonanone <= 4% 4-Nonanol, 2,6,8-trimethyl-

11.12.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2,6,8-Trimethyl-4-nonanone

15.12.2003

2,6,8-Trimethylnonan-4-one

15.12.2003

4-Nonanone, 2,6,8-Trimethyl-

15.12.2003

ECOSOFT Solvent IK

18.12.2003

Isobutyl heptyl ketone (IBHK)

15.12.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = -75.2 °C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2003 (10)

2.2 BOILING POINT

Value : = 218.3 °C at 1013 hPa

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2003 (10)

2.3 DENSITY

Type : density
Value : = .818 g/cm³ at 20 °C

09.10.2003 (10)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .07413 hPa at 20 °C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2003 (10)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 3.96 at °C
pH value :
Method : other (calculated): EPIWIN (v 3.11) KOWWIN Submodel (v 1.67)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Water solubility (mg/L) = 22;
Vapor pressure (mm Hg) = 0.05574;
Boiling point (deg C) = 218.25; and
Melting point (deg C) = -75.15.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

09.12.2003 (12)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 22 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: broadly covered by ASTM method E 1148
Year	:	2000
GLP	:	yes
Test substance	:	other TS

Remark : The liquid-liquid equilibrium measurements were performed in a 0.5 liter glass vessel in a constant-temperature bath. Water and IBHK were added to this vessel through 1/16" lines. The mixture was then stirred vigorously by a magnetic stirrer at the desired bath temperature. Stirring produced very fine droplets of each phase entrained in the other phase, which slowly separated after the liquid was still. After the liquid phases had separated, at least three 10-20 gram samples were withdrawn from both the organic and aqueous liquid phase into weighed glass bottles. A weighed amount of a mixture of toluene and ethylbenzene was added to each vial, and the IBHK was extracted into the toluene-rich phase by vigorously shaking the vial. Ethylbenzene served as the internal standard. An aliquot of the toluene-rich phase was then analyzed by gas chromatography. The concentration of water was found by difference. The hydrocarbon-rich samples were analyzed for water by Karl Fisher titration. 2-Methoxyethanol was added, if necessary, to the sample to prevent a second liquid phase from forming.

The gas chromatographic analyses were performed by an HP5890A gas chromatograph equipped with a DB-1 capillary column. The column was 30 meters long with an internal diameter of 0.32 millimeters and a film thickness of 3 micrometers. Response factors were determined by analyzing gravimetrically prepared standards before each set of samples.

Result : In all samples of the flask shaking test there was excellent separation of the phases. Results were repeated in triplicate. Compositions between 1.0 wt% (10,000 ppm) and 0.1 wt% (1000 ppm) are estimated to be reliable to ±5% of the reported value. The uncertainty increases to ±20% of the reported value as the measured compositions decrease to lower ppm concentrations. The measured value for IBHK was 0.0022 wt% (22 ppm).

Test substance : ECOSOFT Solvent IK: purity > 96 wt. %
This purity is actually measured for isobutyl heptyl ketone + isomers + trimethyl nonanol (CAS RN 123-17-1)

Reliability : (1) valid without restriction
Comparable to guideline study.

Flag : Critical study for SIDS endpoint

09.12.2003 (14)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 82.9 °C
Type :

09.12.2003 (10)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	other: EPIWIN (v 3.11) AOPWIN Submodel (v 1.91)
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 5.5 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	
Method	:	other (calculated): EPIWIN (v 3.11) AOPWIN Submodel (v 1.91)
Year	:	2003
GLP	:	
Test substance	:	
Remark	:	The EPIWIN model estimated the rate constant and atmospheric half-life using the global average for hydroxyl radical concentrations (1.5E6 OH/cm3) and 12hr per day as the duration of the reaction. The EPIWIN model was run using the following measured physical chemical properties: Water solubility (mg/L) = 22; Vapor pressure (mm Hg) = 0.05574; Boiling point (deg C) = 218.25; and Melting point (deg C) = -75.15.
Result	:	Overall OH rate constant = 23.2 E-12 cm3/molecule/sec
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

02.12.2005 (11)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media	:	other: air (emissions to compartment = 1000 kg/hr)
Method	:	Calculation according Mackay, Level III
Year	:	2003
Method	:	Equilibrium Concentration Model (EQC) Level III. The EPIWIN model was run using the following measured physical

chemical properties:
Water solubility (mg/L) = 22;
Vapor pressure (mm Hg) = 0.05574;
Boiling point (deg C) = 218.25; and
Melting point (deg C) = -75.15.

Remark : Level III Fugacity Model (Full-Output):

==========

Chem Name : 4-Nonanone, 2,6,8-trimethyl-
Molecular Wt: 184.32
Henry's LC : 0.000614 atm-m3/mole (calc VP/Wsol)
Vapor Press : 0.0557 mm Hg (user-entered)
Log Kow : 3.96 (Kowwin program)
Soil Koc : 3.74e+003 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	95.8	11	1000
Water	2.89	360	0
Soil	1.09	360	0
Sediment	0.173	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.82e-011	861	137	86.1	13.7
Water	6.86e-012	0.797	0.414	0.0797	0.0414
Soil	3.22e-013	0.301	0	0.0301	0
Sediment	2.28e-012	0.0119	0.000496	0.00119	4.96e-005

Persistence Time: 14.3 hr
Reaction Time: 16.6 hr
Advection Time: 104 hr
Percent Reacted: 86.2
Percent Advected: 13.8

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 11.05
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 2.769 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Result : Concentration (%):
Air - 96
Water - 3
Soil - 1
Sediment - < 1

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2003 (13)

Media : other: water (emissions to compartment = 1000 kg/hr)
Method : Calculation according Mackay, Level III
Year : 2003

Method : Equilibrium Concentration Model (EQC) Level III.

The EPIWIN model was run using the following measured physical chemical properties:

Water solubility (mg/L) = 22;
Vapor pressure (mm Hg) = 0.05574;
Boiling point (deg C) = 218.25; and
Melting point (deg C) = -75.15.

Remark : Level III Fugacity Model (Full-Output):

==========

Chem Name : 4-Nonanone, 2,6,8-trimethyl-
Molecular Wt: 184.32
Henry's LC : 0.000614 atm-m3/mole (calc VP/Wsol)
Vapor Press : 0.0557 mm Hg (user-entered)
Log Kow : 3.96 (Kowwin program)
Soil Koc : 3.74e+003 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.25	11	0
Water	92.2	360	1000
Soil	0.0256	360	0
Sediment	5.52	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.84e-012	324	51.6	32.4	5.16
Water	3.5e-009	407	211	40.7	21.1
Soil	1.21e-013	0.113	0	0.0113	0
Sediment	1.16e-009	6.09	0.253	0.609	0.0253

Persistence Time: 229 hr
Reaction Time: 311 hr
Advection Time: 871 hr
Percent Reacted: 73.7
Percent Advected: 26.3

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 11.05
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 2.769 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Result : Concentration (%):
Air - 2
Water - 92
Soil - <0.1
Sediment - 6

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2003 (13)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic

Inoculum	:	industrial sewage, adapted
Contact time	:	28 day(s)
Degradation	:	= 44.7 (±) % after 28 day(s)
Result	:	other
Control substance	:	Benzoic acid, sodium salt
Kinetic	:	%
		%
Deg. product	:	not measured
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	2004
GLP	:	yes
Test substance	:	other TS

Method : This study investigated the biodegradation of the test substance in closed bottles under aerobic conditions for 28 days. Due to the limited solubility, 21.5 uL (17.0 mg) IBHK was added directly to 2 L of inoculated mineral media and stirred to prepare the test suspensions. The 2 L of inoculated mineral media and IBHK was then combined with 6 liters of inoculated mineral media for a final concentration of 2.14 mg IBHK/L and dispensed into 18-BOD bottles (300 mL). Negative controls (blank), toxicity controls and reference controls (sodium benzoate: 4.02 mg/L) were also prepared, at replicate numbers of 18, 6 and 6, respectively. The flasks were statically incubated at 20.1±0.1°C in the dark. Oxygen in the sealed headspace above each test substance solution was measured on the following study days: 0, 3, 5, 7, 11, 14, 17, 21 and 28. Oxygen from the toxicity and reference controls was measured on study days: 0, 3, 7 and 14.

Remark : Activated sludge was collected from the City of Midland Municipal Wastewater Treatment Plant, Midland, Michigan.

Result :

Incubation Time(days)	%Biodegradation Test Substance	Positive Controls
0	0	0
3	3.2 ± 0.2	68.3 ± 1.9
5	3.6 ± 0.0	
7	3.3 ± 0.2	78.5 ± 1.0
11	7.8 ± 2.3	
14	19.9 ± 2.3	82.3 ± 0.5
17	36.4 ± 1.9	
21	41.2 ± 0.4	
28	44.7 +/- 0.3	

Test substance : See Section 1.1; Purity: 91.33%

Conclusion : Biodegradation achieved a maximum level of 44.7% after 28 days, which according to the OECD guidelines is not considered readily biodegradable.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

01.12.2005 (4)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	>= 1.24
LC50	:	> 1.24
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other
Year	:	2003
GLP	:	yes
Test substance	:	other TS

Method : OECD Guideline No. 203, Fish Acute Toxicity Test.
Directive 92/69/EEC, C.1 Acute Toxicity to Fish.
EPA OTS 797.1440, Fish Acute Toxicity Test.

Remark : Due to the absence of an adequate dose response during the conduct of this study, no statistical analysis programs were used and the LC50 values were empirically determined. The NOEC was determined based on biological interpretation of the data and the highest measured exposure level exhibiting no fish mortality or sublethal effects.

Result : No fish mortality or sublethal effects were observed at or below the highest measured concentration tested of 1.24 mg/L or in the water control during the conduct of this study. The temperature, pH and dissolved oxygen concentration during this study were maintained at 15.2 ± 0.5°C, 7.5 ± 0.2 and 8.3 ± 0.7 mg/l (or >85% saturation), respectively. Pooled standard length and weight means (± sd) for all surviving fish (treatments and controls) were 4.4 ± 0.3 cm and 636 ± 127 mg, respectively.

Test condition : This study evaluated the acute toxicity of the test substance to rainbow trout (Oncorhynchus mykiss) over a 96-hour exposure period under static conditions. A preliminary study found no mortality at nominal concentrations of 0, 5, 10, 50 and 100 mg IBHK/L after 96 hr. Sublethal effects such as lethargy and partial loss of equilibrium were observed at the 50 and 100 mg/L dose levels, however, these effects may have been due to the presence of insoluble test material in the solutions. Test solutions for the definitive study were prepared in duplicate at nominal concentrations of 6.25, 12.5, 25.0, 50.0 and 100 mg IBHK/L. All concentrations were corrected for the 91.3% purity. Duplicate negative control solutions (dilution water) were maintained concurrently. Dilution water was Lake Huron water supplied to the laboratory by the City of Midland Water Treatment Plant, subsequently sand-filtered, pH-adjusted with gaseous CO2, carbon-filtered and UV-irradiated, and monitored regularly. The dilution water used in this study was characterized as follows: hardness of 66-90 mg/L as CaCO3, alkalinity of 40-48 mg/L as CaCO3, pH of 7.3, conductivity of 151-171 mmhos/cm and chlorine <10 ppb. Test vessels were 12-l glass beakers which were filled with 10 l of test solution. Ten fish were impartially introduced to each replicate test vessel at test initiation. Loading did not exceed 1.0-g fish per liter of test solution. Fish were not fed during the study. Terminal body weight and standard length were recorded for all surviving fish at test termination. Fish were observed daily for mortality and sublethal effects. Mortality was defined as a lack of response to prodding of the caudal peduncle accompanied by an absence of opercular movement. Dissolved oxygen (DO), pH and temperature were recorded at test initiation and daily thereafter. Over the course of the study, DO levels averaged 8.3 +/- 0.7, averaged 85% of saturation and remained greater than or equal to 72% over the 96-hour exposure period. The pH averaged 7.5 +/- 0.2 over the course of the study. Temperature in

the test vessels averaged 15.2 +/- 0.5 deg C.

Test substance : IBHK; Lot Number 1229 (Purity 91.3%)

Conclusion : LC50 (24-hr) > 1.24 mg/L;
LC50 (48-hr) > 1.24 mg/L;
LC50 (72-hr) > 1.24 mg/L;
LC50 (96-hr) > 1.24 mg/L; and
NOEC (96-hr) = 1.24 mg/L.

1.24 mg/L represents the maximum solubility of IBHK in this test medium using the test solution preparation procedure employed.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

02.12.2005 (8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : = .949
EC50 : = 3.41
Limit Test : no
Analytical monitoring : no
Method : other
Year : 2003
GLP : yes
Test substance : other TS

Method : OECD Guideline No. 202, Daphnia sp., Acute Immobilization Test, Part 1. Directive 92/69/EEC, C.2 Acute Toxicity for Daphnia.
EPA OTS CFR 797.1300, Daphnid Acute Toxicity Test.

Remark : The U.S. EPA Probit Program, v. 1.5, using nominal IBHK concentrations, was used to calculate the EC50 values and corresponding slope values. If the Probit Program could not be used, the U.S. EPA Trimmed Spearman-Karber Program, v. 1.5, using nominal DIBC concentrations was used to calculate the EC50 values and corresponding percent trim values. The NOEC was determined as the highest exposure concentration that exhibited 0% mortality or sublethal effects.

Result : Immobilization was reported for 40% and 50% of the daphnia at the 11.6 and 9.19 mg/L dose levels at 24 hours. Following 48 hours, immobility was observed in 100%, 95%, 65% and 25% of the daphnia at the 11.6, 9.19, 4.51, and 2.12 mg/L, respectively. The light intensity, temperature, pH and dissolved oxygen concentration during this study were maintained at 1776 ± 34 lux, 20.0 ± 1°C, 7.6 ± 0.1 and 8.9 ± 0.1 mg/L (or >/= 97% saturation), respectively.

Test condition : This study evaluated the acute toxicity of the test substance to <24-hour old daphnia (Daphnia magna Straus) over a 48-hour exposure period under static-renewal conditions. A preliminary study of dose levels 25, 50 and 100 mg IBHK/L found 40 and 50% immobility/mortality at nominal concentrations of 50 and 100 mg IBHK/L, respectively at 24 hours of exposure. Following 48 hours of exposure, immobility increased to 90 and 100% at 50 and 100 mg IBHK/L, respectively. No immobility was observed in the water control. Based on these results, the 48-hour EC50 was estimated to be below the nominal concentration of 25 mg IBHK/L. Due to the results of this preliminary study, the test solutions for the definitive study were prepared in duplicate at nominal concentrations of 1.56, 3.13, 6.25, 12.5, 25.0, 50.0, and 100 mg IBHK/L. All concentrations were adjusted for the purity of 91.3%. Duplicate negative control solutions (dilution water) were maintained concurrently. Dilution water was Lake

Huron water supplied to the laboratory by the City of Midland Water Treatment Plant, subsequently sand-filtered, pH-adjusted with gaseous CO2, carbon-filtered and UV-irradiated, adjusted to hardness of about 170 mg/L as CaCO3, then autoclaved at 250°F and 18 psi for 30 min. The dilution water used in this study was characterized as follows: hardness of 158-174 mg/L as CaCO3, alkalinity of 36-38 mg/L as CaCO3, pH of 7.6 ± 0.1, conductivity of 417-434 mmhos/cm and chlorine <10 ppb. Test vessels were 250-ml glass jars containing 200 ml of test solution. Ten daphnia were impartially introduced to each replicate test vessel at test initiation. Daphnia were observed every 24 hours for immobility, mortality and any other sublethal effects. Immobility was defined as the inability to swim within 15 seconds after gentle agitation of the test container. Dissolved oxygen, pH and temperature were recorded every 24 hours.

Test substance : IBHK; Lot Number 1229 (Purity 91.3%)

Conclusion : A 24-hour EC50 could not be calculated using the U.S. EPA Probit or Trimmed Spearman-Karber statistical programs due to the insufficient biological response following 24 hours of exposure.
EC50 (48-hr) = 3.41 mg/L (95% confidence interval = 2.71-4.20 mg/L; Probit slope = 4.1 with 95% confidence interval of 2.8-5.4); and
NOEC (48-hr) = 0.949 mg/L.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

02.12.2005 (7)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae: Pseudokirchneriella subcapitata

Endpoint : other

Exposure period : 96 hour(s)

Unit : mg/l

NOEC : = 1.3

EC50 : > 1.3

Limit test : no

Analytical monitoring : yes

Method : other

Year : 2003

GLP : yes

Test substance : other TS

Method : OECD Guideline No. 201, Algal Growth Inhibition Test.
Directive 92/69/EEC C.3: Algal Inhibition Test.
EPA OTS 797.1500, Algal Acute Toxicity Test.

Remark : Nominal concentrations of IHBK were used for all calculations. The EC50 values were not calculated due to less than 50% effect at both 72 and 96 hours. The cell density, growth rate and biomass data was tested for normality and homogeneity of variance using the Shapiro-Wilk's Test and the Bartlett's Test, respectively. As all the data at both time points met the criteria for homogeneity and normality, additional statistical tests, analysis of variance and Dunnett's test, were performed to determine NOEC values.

Result :

Test Endpoint	Hours	EC50	NOEC (mg/L)
Cell Density	72	>1.03 mg/L	1.03
Cell Density	96	>1.03 mg/L	1.03
Biomass *	72	>1.03 mg/L	1.03
Biomass *	96	>1.03 mg/L	1.03
Growth Rate	0-72	>1.03 mg/L	1.03
Growth Rate	0-96	>1.03 mg/L	1.03

* Biomass = area under the growth curve.

Test condition : This study evaluated effects of the test substance on growth of the green

alga, Pseudokirchneriella subcapitata, over a 96-hour exposure period under static conditions. In the range-finding test of nominal concentrations 0.100, 1.00, 10.0 and 100 mg/L, the percent inhibition was -5, -11, 12, and 28% after 96 hours of exposure. Based on this, the 4-day EC50 value was >100mg IBHK/L. The dose levels selected for the definitive test were 3.13, 6.25, 12.5, 25.0, 50.0, and 100 mg IBHK/L algal assay medium (AAM). IBHK exhibited poor solubility in AAM, so a saturated stock solution at a nominal concentration of 1000 mg IBHK/L AAM was made and the test solutions were dilutions of the stock. Negative control solutions (medium only) were also maintained concurrently. All test solutions were adjusted for 91.3% purity. Test vessels were 250-mL Erlenmeyer flasks with Shimadzu closure and contained 100 mL of test solution. Each of four replicates per treatment and control were inoculated with 3-7 day old algal culture to achieve 10,000 cells/mL. Treatment and control solutions were incubated in a growth chamber at 24 ± 2°C under continuous illumination at 8000 ± 1600 lux. Temperature and pH were recorded at test initiation and termination. Cell numbers were measured daily by electron particle counting. Cell density, biomass (as area under the growth curve) and growth rate were calculated from cell counts.

Test substance : IBHK; Lot Number 1229 (Purity 91.3%)

Conclusion : No effects were seen at the highest measured test concentration (1.03 mg IBHK/L), which was likely below the water or media solubility of IBHK. This test provides adequate data to assess the risk of IBHK to aquatic algal species.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

02.12.2005 (5)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 8470 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	40
Vehicle	:	other: Tergitol 7
Doses	:	6300, 7950, 10000 and 12600 mg/kg
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS
Remark	:	A 20% dispersion of the test substance in 1% Tergitol 7 was administered by gavage to 10 male albino rats per group. Doses were 6300, 7950, 10000 and 12600 mg/kg body weight. Animals were observed for 14 days following dosing. Body weights were obtained on the day of dosing and on day 14.
Result	:	LD50 = 8470 mg/kg (95% confidence limits = 7180 to 9990 mg/kg) High doses resulted in prostration and narcosis, with lung hemorrhages, congested livers, pale kidneys and opacity of the intestine notable on autopsy. Death was delayed for 72 hours or more in most cases. All surviving animals gained weight 14 days following dosing. The number of deaths are indicated in the following table:

Dose (mg/kg)	Number dead/number dosed
6300	3/10
7950	4/10
10000	6/10
12600	10/10

Test substance	:	Trimethyl nonanone
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

15.12.2003 (2)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: saturated vapor
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Doses	:	substantially saturated vapor
Exposure time	:	8 hour(s)
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	other TS

Method	:	Six rats were exposed to the test substance as a saturated vapor generated at room temperature for 8 hours.
Result	:	Two of the six rats died in 8 hours. The cause of death was considered to be direct damage to the lung, as revealed by marked congestion.
Test substance	:	Trimethyl nonanone

15.12.2003 (2)

Type	:	other
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Doses	:	cooled mist
Exposure time	:	1 hour(s)
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS

Remark	:	Six rats were exposed to the test substance as a cooled mist prepared by heating the aerated test substance to 170 degrees C.
Result	:	Exposure to a cooled mist was lethal to all of 6 rats in one hour and 0 of 6 rats in 30 minutes. The cause of death was considered to be direct damage to the lung, as revealed by marked congestion.
Test substance	:	Trimethyl nonanone

15.12.2003 (2)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 9030 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	male
Number of animals	:	40
Vehicle	:	other: none
Doses	:	7950, 10000, 12600 and 15800 ml/kg
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS

Remark	:	The undiluted test substance was applied as a single dose to 4 groups of 10 male albino rabbits each at the following dose levels: 7950, 10000, 12600 and 15800 ml/kg, which correlates to doses of 6500, 8180, 10300 and 12900 mg/kg, respectively (density = 0.818 g/cm3). The test material was applied, undiluted at the appropriate dose, under an impervious sheeting. The animals remained exposed to the test substance for 24 hours. Rabbits were observed for 14 days and body weights were obtained on the day of application and on day 14.
Result	:	LD50 = 9030 mg/kg (95% confidence limits = 7710 to 10590 mg/kg) Erythema and occasionally necrosis of the skin resulted from the dose. The animals were sensitive to handling for a period of one week after the application. All but 2 animals (one each in the 10300 and 6500 mg/kg dose groups) lost weight during the 14 day post-application period. The weight losses may have been attributed in part to persistent diarrhea. The number of deaths are indicated in the following table:

Dose (ml/kg)	Number dead/number dosed
7950	2/10
10000	4/10
12600	5/10
15800	9/10

Test substance : Trimethyl nonanone
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.12.2003 (2)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type :
Species : rat
Sex : male/female
Strain : other: CD
Route of admin. : gavage
Exposure period : See Section 5.8.1
Frequency of treatm. : See Section 5.8.1
Post exposure period : See Section 5.8.1
Doses : 100, 300, 1000 mg IBHK/kg/day
Control group : yes, concurrent vehicle
Method : other: OECD 422 and US EPA OPPTS 870.3650
Year : 2005
GLP : yes
Test substance : other TS

Method : See Section 5.8.1
Remark : NOAEL = 100 mg/kg bw - females; none determined - males
Result : See Section 5.8.1
Test substance : IBHK; lot RA1055T628 (91.2% Purity)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
02.12.2005 (1)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Chromosomal aberration test
System of testing : Rat Lymphocytes
Test concentration : 0, 9.4, 18.75 and 37.5 ug/ml (without S-9 for 4 hours treatment); 0, 100, 110 and 120 ug/ml (with S-9 for 4 hours); and 0, 40, 50 and 60 ug/ml (without S-9 for 24 hours).

Cycotoxic concentr.	:	9.4-75 ug/ml, 4 hours with and without S-9; >=75 ug/ml, at 24 hours without S-9
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	OECD Guideline No. 473, Genetic Toxicology: In vitro Mammalian Cytogenetic Test. EPA OPPTS 870.5375, In vitro Mammalian Chromosome Aberration. Directive EC B.10, 2000, Mutagenicity: In vitro Mammalian Chromosomal Aberration Test.
Remark	:	The criteria for evaluation were significant dose-related and reproducible increase in the frequency of cells with aberrations.
Result	:	The four hour treatment assay, with and without metabolic activation, had reductions in mitotic indices at concentrations of 9.4-75 ug/ml. The remaining higher concentrations had no mitoses suggesting toxicity. Without S-9, after 24 hours treatment, excessive toxicity was apparent starting at 75 ug/ml and the higher groups had no mitoses present. The lower concentrations had reduced mitoses. For chromosomal aberration determination, the concentrations were lowered to decrease toxicity. In treatment groups for 4 hours with and without S-9 and 24 hours without S-9, the frequency of chromosomal aberrations was increased as compared to the control but the difference was not significant.
Test condition	:	Blood samples were collected from male rats by cardiac puncture. In each assay, the blood samples were pooled and whole blood cultures were set up by the addition of the appropriate medium and supplements. Cell cultures were treated for 4 hours in the presence and absence of Aroclor™-induced rat liver (S-9 mix) and for 24 hours without the S-9 mix at dose concentrations ranging from 0 to 600 ug/ml of test substance. Based on the mitotic indices, the following concentrations were used to determine chromosomal aberrations: 0, 9.4, 18.75 and 37.5 ug/ml (without S-9 for 4 hours treatment), 0, 100, 110 and 120 ug/ml (with S-9 for 4 hours), and 0, 40, 50 and 60 ug/ml (without S-9 for 24 hours). All test assays were performed along with concurrent vehicle and positive controls. Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the negative control. For the non-activation assay, Mitomycin C was the positive control substance: The positive control substance cyclophosphamide was used in the activation assay. After the incubations, the cells were washed, swollen by hypotonic treatment, fixed to slides and stained. The cells were scored for structural chromosomal abnormalities, such as chromatid and chromosome gaps and chromatid breaks and exchanges.
Test substance	:	See Section 1.1; Purity: 91.2%
Conclusion	:	Isobutyl heptyl ketone is not considered genotoxic in this test.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.03.2005 (6)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537; Escherichia coli tester strain WP2uvrA.
Test concentration	:	Prelim: 1, 3.3, 10, 33, 100, 333, 1000, 3333, and 5000 ug/plate Mutagen:0.33, 1.0, 3.3, 10.0, 33.0, 100, 1000, 5000 ug/plate (TA100) 33.0, 100, 333, 1000, 3333, 5000 ug/plate (all other test strains)
Cycotoxic concentr.	:	Prelim: >33 ug/plate, without S-9, >333 ug/plate with S-9: TA100; >33 ug/plate, without S-9: TA1537. Mutagen: >33 ug/plate, with and without S-9: TA100; >/= 100 ug/plate, without S-9: TA1537.

Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	OECD Guideline No. 471, Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay. EPA OPPTS 870.5100, E. coli WP and WP2uvrA Reverse Mutation Assay. EC OJ No. L 136.
Remark	:	The criteria for evaluation were: at least a 2-fold (TA-100) or 3-fold (TA98, TA1535, TA1537, and WP2uvrA) concentration-related increase and reproducible increase in mean revertants per plate over the mean of the appropriate vehicle control was considered positive.
Result	:	In the preliminary assay, evidence of cytotoxicity was observed in TA100 from 33 and 333 ug/plate with and without exogenous metabolic activation. TA1537 exhibited cytotoxicity at 33 ug/plate in the presence of S-9 only. There was no increase in the mutant counts for any strain at any dose level with or without the presence of S-9. In the mutagenic assay, TA100 exhibited cytotoxicity at dose levels >33 ug/plate in both the presence and absence of S-9. TA1537 also exhibited cytotoxicity at >/= 100 ug/plate, but only in the absence of S-9. There were no increases in the number of revertants per plate for any of the tester strains either in the absence or presence of S-9 at the concentrations examined.
Test condition	:	The preliminary assay was conducted with nine concentrations of IBHK, 1-5000 ug/plate, in both the presence and absence of microsomal enzymes prepared from Aroclor™-induced rat liver (S9 mix) along with concurrent vehicle and positive controls using three plates per concentration. Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the negative control. The tester strains were exposed via the pre-incubation method, in which the tester strains and test material were pre-incubated at 37ºC for approximately 20 minutes before the addition of molten agar. All concentration levels of the test article, negative controls and positive controls were plated in triplicate. The mutagenicity assay, by the pre-incubation method, was conducted at levels 0.33-500 ug/plate, eight concentrations, for TA100, due to the demonstrated cytotoxicity in the preliminary assay, and 33-5000 ug/plate, six concentrations, for the remaining strains. All concentration levels of the test article, negative controls and positive controls were plated in triplicate. Prior to scoring, the tester strains were evaluated for the proper genetic markers. The condition of the bacterial background lawn was evaluated for evidence of cytotoxicity and test article precipitate. Cytotoxicity was scored relative to the vehicle control and recorded with revertant counts.
Test substance	:	See Section 1.1; Purity: 91.2%
Conclusion	:	No increase in revertants meeting the criteria for positive response was observed at any concentration in any strain with or without metabolic activation in either experiment. Under the conditions of this study, IBHK was not mutagenic to bacterial cells with or without metabolic activation.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.03.2005 (3)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type	:	other
Species	:	rat
Sex	:	male/female
Strain	:	other: CD
Route of admin.	:	gavage
Exposure period	:	Males- 2 weeks prebreeding, two weeks breeding and 10 days post-breeding Females- 2 weeks prebreeding, two weeks breeding, through gestation (3 weeks) and lactation (4 days)
Frequency of treatm.	:	once daily
Premating exposure period		
Male	:	2 weeks
Female	:	2 weeks
Duration of test	:	males 10 days post-mating; females lactation day 4.
No. of generation studies	:	2
Doses	:	100, 300 and 1000 mg IBHK/kg/day
Control group	:	yes, concurrent vehicle
other:NOEL	:	= 300 mg/kg bw
Reproductive other:NOEL	:	= 1000 mg/kg bw
Neurological		
Method	:	other
Year	:	2005
GLP	:	yes
Test substance	:	other TS
Remark		NOAEL females = 100 mg/kg bw; no NOAEL for males established.

Method	:	OECD Guideline No. 422, A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. U.S. EPA OPPTS 870.3650, Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test.
Remark	:	STATISTICAL ANALYSIS: Descriptive statistics (means and standard deviations) were reported for RBC indices and WBC differential counts. Parental body weights, gestation and lactation body weight gains, litter mean body weights, feed consumption, urine volume, urine specific gravity, coagulation, clinical chemistry data, appropriate hematologic data and organ weights (absolute and relative) were first evaluated by Bartlett's Test for equality of variances. Based on the outcome, a parametric or nonparametric test analysis of variance (ANOVA) was performed. If the ANOVA was significant (alpha=0.05), then a Dunnett's Test or the Wilcoxon Rank-Sum Test with Bonferroni's correction was performed. The mean pup body weights for postnatal day (pnd) 1 and 4 were analyzed with an analysis of covariance (ANCOVA), where the covariate was litter size on pnd 1 and 4 respectively. The ANCOVA was run first with the interaction between dose and the covariate included. If the interaction was not significant, the analysis was run again without the interaction. If the dose effect was significant at alpha=0.05 in the second run, the least square means were calculated and the dosed groups were compared to the control groups by a t-test. The gestation length, average time to mating and litter size were examined with a non-parametric ANOVA. If there was significance, the Wilcoxon Rank Sum Test with Bonferroni's correction was performed. Statistical outliers were identified by a sequential method and were only excluded from the analysis for documented, scientifically sound reasons. The mating, conception, fertility and gestation indices were analyzed by the Fisher exact probability test with Bonferroni's correction. Evaluation of the neonatal sex ratio on lactation day (ld) 1 was performed by the binomial distribution test. Survival indices, post-implantation loss and pother

incidence data among neonates were analyzed using the litter as the experimental unit by the censored Wilcoxon test as modified by Haseman and Hoel with Bonferroni's correction.
DCO and sensory evaluation incidence scores were statistically analyzed by a z-test of proportions comparing each treated group to the control.
Data collected at each time point were analyzed separately.
Rectal temperature and grip performance were analyzed by ANCOVA with exposure as the factor and the covariate of the pre-exposure time point measure of the variable. The first examination of the ANCOVA was for the treatment by pre-exposure measure interaction and if this was significant, then an ANVOA was run separately for each time point. If the dose effect was significant, the least square means were generated and a t-test performed.
Motor activity counts were reported as their square roots and analyzed by a repeated-measure design with treatment as the factor and the repeated factor of time. Motor activity also had the repeated factor of epoch (within time) in the model. The inclusion of pre-exposure data in the analysis made relevant only the analyses that included factors of both treatment and time. The primary interactions examined were treatment-by-time and treatment-by-time-by-epoch. Linear contrasts were calculated to determine which treatment groups differed from the control if either of these interactions were significant. The probability values were reported without correction.

Result : ANALYTICAL ANALYSIS

-Concentrations: Analyses of the dosing concentrations from the initial preparation indicated mean concentrations of IBHK ranging from 92.4-94.9% of the targeted concentrations.
-Stability: IBHK was found to be stable for 28 days in corn oil at concentrations ranging from 2.5-25.0 mg/ml.
-Homogeneity: Analysis of aliquots removed from the low and high dose groups confirmed that IBHK was homogenously distributed throughout the dose suspension.

PARENTAL TOXIC EFFECTS BY DOSE LEVEL:
-Mortality and day of death: none

-In-Life Observations: Oral administration of IBHK resulted in increased salivation (perioral staining - clear) at all dose levels in both sexes. Salivation was transient, usually ending within one hour of dosing, suggesting a local response to the taste of the test material.

Perineal urine soiling was increased in males in the 1000 mg IBHK/kg/day group.

Salient Male Clinical Observations

Male Clin Obs	Dose Level (mg/kg/day)			
(# Animals Affected)	0	100	300	1000
Perioral Soiling - Clear	1	7*	11*	12*
Perineal Soiling - Urine	0	0	0	4*

* indicates effects considered to be treatment-related.

Salient Female Clinical Observations

Female Clin Obs	Dose Level (mg/kg/day)			
(# Animals Affected)	0	100	300	1000
Perioral Soiling - Clear	2	8*	12*	12*

* indicates effects considered to be treatment-related.

-Detailed Clinical Observations: Except as noted above, examinations performed on all rats revealed no treatment-related or statistically significant findings in the treatment groups as compared to the control group in either sex.

-Body weight/body weight gain: No significant differences in body weight or weight gain were observed for males at ant any test level during the ~ 6 weeks of exposure. There were also no treatment-related significant differences in the body weights or body weight gains of females at any dose level tested during the pre-mating, gestation or lactation periods.

-Feed Consumption: There were no significant differences in feed consumption between control and test animals in either sex.

-Reproductive Indices, Pup Survival and Sex Ratio: There were no treatment-related effects at any dose level on any of the reproductive parameters, pup survival indices or sex ratio that were evaluated. Pup survival was significantly higher than controls on Id 1 in the 300 and 1000 mg/kg/day dose groups; however, this finding is attributed to the lower value in the control group and was not considered adverse. There was a small, statistically significant decrease in gestation length of the 100 and 1000 mg/kg/day dose groups. However the value was within the range of the historical control data and not considered to be treatment-related.

Significant Effects on Gestation Length

Gestation Length Parameter (mean)	Dose Level (mg/kg/day) 0	100	300	1000
Days	22.1	21.5*	21.6	21.5*

* Statistically different from control mean by Wilcoxon's test, alpha=0.05

Historical Control Data for Gestation Length

Study # / Year	1 2000	2 2003	3 2004	4 2004	Range (Average)
Gestation Length (Days)	21.8	21.6	21.5	21.3	21.3-21.8 (21.6)

-Litter Observations: Observations recorded in the offspring occurred at low frequency and bore no relationship to treatment. One low-dose pup was observed with hindlimb rotation, but this was an isolated occurrence bearing no relationship to treatment.

-Litter Size and Pup Body Weights: Decreases in pup body weights of male and female pups on pnd day 1 and 4 in the 1000 mg/kg/day dose group were initially identified as being statistically different from controls using an ANOVA, however, due to the increased litter size in the high-dose group, an ANCOVA was used to determine if the difference in pup body weight was due to litter size and not treatment. The ANCOVA indicated that the effects on pup body weight were not significant on pnd 1 but were significant on pnd 4.

Significant Effects on Mean Pup Weights

Mean Pup Weights Parameter (mean) Values	Dose Level (mg/kg/day) 0	100	300	1000

pnd 1 Female (g)	7.0	6.5	6.5	6.1a
pnd 1 Male (g)	7.4	6.9	6.8	6.4a*
pnd 4 Female (g)	10.1	9.1	9.1	8.3a*
pnd 4 Male (g)	10.7	9.5	9.5	8.5a*

a = indicates effects considered to be treatment related.
* Statistically different from control mean by Dunnett's test, alpha=0.05

FUNCTIONAL TESTS
-Sensory Evaluation: Examinations of males and females at termination revealed no treatment-related findings.
-Rectal Temperature: Treatment did not affect the rectal temperature of either sex.
-Grip Performance: There were no treatment-related effects on the hindlimb or forelimb grip performance in either male or female rats.
-Motor Activity: Treatment did not affect total motor activity count in either sex. The distribution of the motor activity counts within a session were also not affected by treatment in males, however, was statistically different for the females. For interpretation of this statistically significant triple interaction, additional examination of the data was performed. All of the double interactions containing treatment, time or epoch were examined, indicating that there was a significant difference in time-epoch, but that it was due to a difference in days not treatment. The female data for overall count distributions for the four treatment groups displayed differences from baseline and post-treatment conditions, irrespective of treatment. Linear contrasts indicated that that triple interactions were not statistically significant and the p values do not support a dose-response relationship. The interpretation of these data led to the conclusion that the statistically significant triple interaction in female rats represents a difference between days rather than an effect of treatment.

CLINICAL PATHOLOGY
-Hematology: Males given 300 or 1000 mg/kg/day had hemoglobin levels that were slightly lower (statistically significant) than the controls. The differences were not considered treatment-related as they were within, or in close proximity to, the historical control range.

Salient Hematology Finding

Sex	Males			
Dose (mg/kg/day)	0	100	300	1000
Hemoglobin (g/dl)	15.6	15.1	15.0*	14.9*

* Statistically significant from control mean by Dunnett's test, alpha=0.05

Historical Control Data for Hematology

Study # (year)	1 (2000)	2 (2003)	3 (2004)	4 (2004)
Male				
Hemoglobin (mg/dl)	15.0	15.8	15.1	15.5

-Coagulation: The prothrombin time for males in the 1000 mg/kg/day dose group was higher than controls, statistically significant and outside of the historical control range.

Salient Coagulation Findings

Sex	Males			
Dose (mg/kg/day)	0	100	300	1000
Prothrombin time (sec)	13.1	13.2	13.7	15.8a*

a = indicates effects judged to be treatment-related.
* Statistically significant from control mean by Dunnett's test, alpha=0.05

-Clinical Chemistry: Serum cholesterol levels in males and females in the 1000 mg/kg/day group were statistically higher than the control and slightly outside of the historical control range. The differences were considered to possibly be treatment-related, but not toxicologically significant because increase compared to the historical control data (43-58 mg/dl for males and 42-73 mg/dl for females) was minor. The AST and total protein of males in the 1000 mg/kg/day group were higher and lower, respectively, than the control values and statistically identified. Alterations in AST were considered treatment-related, but secondary to the hepatocellular hypertrophy noted in the necropsy of these animals. ALP activity in the 1000 mg/kg/day females was lower than the control and historic values (66-97 u/l). While this was considered treatment related, it was not considered toxicologically significant due to the minor nature of the difference and lack of apparent adverse effects. The urea nitrogen values of males in the 300 and 1000 mg/kg/day groups was marginally higher than that of control; however, the differences were minor, within the historic range (13-14 mg/dl) and not considered treatment-related. Females given 100 mg/kg/day had significantly lower albumin than controls, but this was not considered treatment-related as the higher dose groups did not display similar responses.

Salient Clinical Chemistry Findings

Sex	Males				Females			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
CHOL (mg/dl)	42	45	48	61a*	53	52	63	74a*
AST (u/l)	97	86	83	77a*	108	90	107	98
Total Protein (g/dl)	6.5	6.5	6.5	7.0a*	6.5	6.3	6.6	6.7
Albumin (g/dl)	3.4	3.3	3.3	3.5	3.4	3.3*	3.4	3.5
ALP (u/l)	142	132	156	127	91	84	100	64a**
Urea Nitrogen (mg/dl)	14	14	16*	15*	17	19	18	18

* Statistically significant from control mean by Dunnett's test, alpha=0.05.
** Statistically significant from control mean by Wilcoxon's test, alpha=0.05.
a = indicates the effects judged to be treatment-related.

-Urinalysis: The urine pH of males in the 1000 mg/kg/day dose group was more acidic than the controls and the ketone levels were slightly lower than the control levels. These differences were outside the historical control range and considered to be to be treatment-related. A few males in the 300 mg/kg/day group also had slightly more acidic urine pH. This acidic urine pH could be secondary to the degenerative changes in the kidneys of the males, but could also be associated with the acidic metabolites of IBHK.

Salient Urinalysis Findings

Sex	Males			
Dose (mg/kg/day)	0	100	300	1000
Urine pH	7.0 (2)	7.0 (3)	6.5 (2)*	6.1 (1)*
	7.5 (3)	7.5 (4)	7.0 (3)	6.5 (9)*
	8.0 (3)	8.0 (3)	7.5 (6)	7.0 (2)
	8.5 (3)	8.5 (4)	8.0 (1)	
	9 (1)			
Urine Ketones				Neg (1)*
	Trc (4)	Trc (4)	Trc (4)	Trc (7)*
	+ (8)	+ (8)	+ (8)	+ (4)

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* indicates the effects judged to be treatment-related.
Urine pH and urine ketone data tabulated as number of animals (N) with the stated value.
Trc Trace Neg Negative

ANATOMIC PATHOLOGY
-Organ Weights: Dose-related increases in absolute and relative liver weights occurred in males and females given 100, 300 or 1000 mg/kg/day. Absolute and/or relative kidney weights of males and females given 300 or 1000 mg/kg/day were also increased. These differences were statistically identified and outside of the historical control data. Therefore, the differences were considered to be treatment-related.
Absolute and/or relative thyroid weights of males given 100 or 1000 mg/kg/day and females given 300 or 1000 mg/kg/day were higher than control weights and were statistically identified, higher than historical control data and considered to be treatment-related. The relative weight of the ovaries of the females given 100 mg/kg/day was significantly increased as compared to controls and increased as compared to the historical data. However, this difference was not considered to be treatment-related given the normal reproductive performance of these females, lack of any histological changes, and the minor difference from controls. In addition, the absolute and relative ovarian weights from all dose levels in this study, including controls, were lower than historical controls.

Salient Organ Weights

Sex	Males			
Dose (mg/kg/day)	0	100	300	1000
Terminal Body (g)	390.5	400.3	394.1	385.9
Liver (g)	11.269	13.044a*	14.005a*	17.678a*
Liver (g/100)	2.871	3.262a*	3.557a*	4.581a*
Kidney (g)	2.868	3.035	3.591a*	4.222a*
Kidney (g/100)	0.736	0.758	0.912a**	1.096a**
Thyroid (g)	0.0164	0.0193*	0.0186	0.0222a*
Thyroid (g/100)	0.0042	0.0048	0.0047	0.0058a*

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* Statistically significant from control mean by Dunnett's test, alpha=0.05.
** Statistically significant from control mean by Wilcoxon's test, alpha=0.05.
a = indicates the effects judged to be treatment-related.
g/100 = organ weight per 100 grams of body weight

Sex	Females			
Dose (mg/kg/day)	0	100	300	1000
Terminal Body (g)	272.0	273.2	273.2	259.8
Liver (g)	9.810	10.802a	12.077a*	14.167a*
Liver (g/100)	3.612	3.944a*	4.417a*	5.445a*
Kidney (g)	1.934	1.992	2.110	2.121
Kidney (g/100)	0.712	0.726	0.770a*	0.817a*
Thyroid (g)	0.0143	0.0162	0.0177a*	0.0196a*
Thyroid (g/100)	0.0053	0.0059	0.0065a*	0.0076a*
Ovaries (g)	0.113	0.126	0.126	0.128*
Ovaries (g/100)	0.042	0.046	0.046	0.049*

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* Statistically significant from control mean by Dunnett's test, alpha=0.05.
** Statistically significant from control mean by Wilcoxon's test, alpha=0.05.
a = indicates the effects judged to be treatment-related.
g/100 = organ weight per 100 grams of body weight

-Gross Pathology: There were no treatment-related gross pathologic

observations.
-Histopathology: Male rats given 100, 300 or 1000 mg/kg/day had degenerative kidney effects that were in excess of that observed in the control male rats and were interpreted to be treatment related. Male rats given 1000 mg/kg/day had degenerative changes involving the renal tubules that were slight to moderate in severity compared with controls. This lesion primarily involved the proximal convoluted tubules and was characterized by an increase in cytoplasmic basophilia of tubular epithelial cells, thickening of the tubular basement membrane, presence of granular casts within the tubular lumens and the interstitial accumulation of mononuclear inflammatory cells. Necrotic tubular epithelial cells were also noted in the majority of males given the 1000 mg/kg/day were multifocal in distribution and very slight in severity. Male rats given 300 mg/kg/day had similar degenerative tubular changes of slight to moderate severity, and some of these rats had a very slight necrosis of tubular epithelial cells. Male rats given 0 or 100 mg/kg/day had a very slight tubular degeneration that was similar to the degeneration seen in the males of the higher dose groups. This slight degeneration occurred in 3 of 12 control males as compared to 7 of 12 males given 100 mg/kg/day. The increased incidence of this observation in males given 100 mg/kg/day was considered to be treatment-related. Degenerative kidney lesions were noted in females given 0 or 1000 mg/kg/day but were interpreted to be spontaneously occurring because of the low incidence and minimal severity.
Male rats given 100, 300 or 1000 mg/kg/day also had eosinophilic staining (hyalin) cytoplasmic inclusions/droplets in the proximal tubules, which were infrequently observed in the control males, not observed in any of the females and was interpreted to be treatment-related. The results were consistent with, but not diagnostic for, alpha 2u globulin accumulation. Increased levels of this protein in the proximal convoluted tubular cells of male rats has been shown to cause tubular degeneration, although this is not considered relevant for human risk assessment as humans do not develop nephropathy due to differences in this protein.

Treatment-Related Kidney Effects

Sex	Males				Females			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Kidneys (# examined)	12	12	12	12	12	0	0	12
Degeneration, tubule, multifocal:								
very slight	3	7*	3	2	1	-	-	3
slight	0	0	6*	3*	0	-	-	0
moderate	0	0	3*	7*	0	-	-	0
Necrosis, individual cell, tubule, multifocal:								
very slight	0	0	4*	7*	0	-	-	0
Hyalin droplet formation, tubule:								
very slight	1	12*	2	0	0	-	-	0
slight	0	0	10*	12*	0	-	-	0

- No data, tissues not examined
* indicates the effects judged to be treatment related.

Males given >/= 100 mg/kg/day and females given >/= 300 mg/kg/day had treatment-related hypertrophy of hepatocytes in the liver. The effect was more prominent in males, given that it was seen even at the lowest dose point and based on the panlobular distribution within the hepatic lobule.

Treatment-Related Liver Effects

Sex	Males				Females			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Liver (# examined)	12	12	12	12	11	12	12	12
Hypertrophy, hepatocyte, centrilobular/midzonal, with altered tinctorial properties:								
very slight	0	0	0	0	0	0	11*	0
slight	0	0	0	0	0	0	0	12*
Hypertrophy, hepatocyte, panlobular, with altered tinctorial properties:								
very slight	3	10*	10*	4	0	0	0	0
slight	0	0	2*	8*	0	0	0	0

* indicates the effects judged to be treatment related.

Males given >/=100 mg/kg/day had treatment-related hypertrophy of follicular epithelial cells of the thyroid gland. Thyroid effects were not observed in female rats.

Treatment-Related Thyroid Effects

Sex	Males				Females			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Thyroid gland (# examined)	12	12	12	12	12	1	0	12
Hypertrophy, follicle cell:								
slight	1	6*	9*	12*	0	0	-	0

- No data, tissues not examined.
* indicates the effects judged to be treatment related.

Test condition : TEST ORGANISMS
-Male and female CD rats
-Age: ~8 weeks of age
-Number of animals: 48 females and 48 males (12 sex/group)
ADMINISTRATION/EXPOSURE
-Route: oral/gavage
-Doses: The target doses were 0, 100, 300 and 1000 mg IBHK/kg/day. IBHK was administered in a corn oil suspension and samples were analyzed to confirm homogeneity, stability and concentration verification.
-Exposures: Once Daily
Males- 2 weeks prebreeding, two weeks breeding and 10 days post-breeding
Females- 2 weeks prebreeding, two weeks breeding, through gestation (3 weeks) and lactation (4 days)

PARAMETERS ASSESSED DURING STUDY:
-Clinical observations performed and frequency: Clinical observations were conducted daily throughout the study period.
-Detailed Clinical Observations (DCO): Conducted on all rats ore-exposure and weekly throughout the study. Mated females received DCO examinations on gestation day (gd) 0, 7, 14 and 20, and lactation day (ld) 4. The DCOs included cage-side, hand-held and open-field observations that were recorded categorically or using explicitly defined scales.
-Functional Tests: The functional tests included a sensory evaluation (nociception and startle response), rectal temperature, grip performance and motor activity.
-Body weight/body weight gain: All rats were weighed at least once in the pre-exposure period. Male body weights were recorded weekly throughout

the study. Female body weights were performed weekly for the premating and mating periods. Maternal body weights were recorded on GD 0, 7, 14, 17 and 20. Females that delivered were weighed on ld 1 and 4. Females that failed to mate or deliver were weighed on a weekly basis for the study duration.
-Food consumption: Food consumption was determined weekly for males and females during the pre-mating period. Due to co-housing, food consumption was not measured during mating. Following breeding, food consumption was not measured for the males. During gestation, food consumption for the females was measured on gd 0, 7, 14, 17 and 20. After parturition, food consumption was measured on ld 1 and 4. Food consumption was not recorded for females that did not mate or deliver.
-Breeding Procedures: During the 2 week mating period, one male and one female from the same dose group were co-habitated until pregnancy occurs or the mating period is over. Females were examined daily for a vaginal copulatory plug or the vaginal presence of sperm determined by vaginal lavage samples. If pregnancy was not determined by the end of the mating period, the animals were separated and housed individually for the remainder of the study.
-Litter Data: Females were observed for signs of parturition beginning on gd 20. The first day the presence of a litter was noted was designated ld 0. All litters were examined as soon as possible after delivery and the following information was recorded: date of parturition, litter size on gd 0, the number of live and dead pups on gd 0, 1 and 4 post-partum and the sex and weight of each pup on postnatal day (pnd) 1 and 4. Pup clinical observations were recorded on pnd 0, 1 and 4. In addition, any physical abnormalities or demeanor changes were recorded during the lactation period. Any pups found dead were sexed, examined grossly for external and visual effects, if possible and discarded.

PATHOLOGY
-Clinical Pathology: On the day prior to necropsy, all animals were fasted overnight. At necropsy, animals were anesthetized with carbon dioxide and blood samples were removed from the orbital sinus. Blood samples were not taken from females that failed to deliver a litter.
----Hematology Assays: hematocrit (HCT), hemoglobin concentration (HgB), red blood cell (RBC) count, total white blood cell (WBC) count, platelet (PLAT) count, differential WBC count, and red blood cell indices including mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC).
----Coagulation Assay: prothrombin time (PT).
----Clinical Chemistry Assays: Enzyme activities of alkaline phosphatase (AP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and concentrations of: albumin (ALB), cholesterol (CHOL), creatinine (CREAT), electrolytes (Na, K, PO4, Cl and Ca), glucose (GLU), total bilirubin (TBIL), total protein (TP), and urea nitrogen (UN).
Urine was collected from all male rates in each dose group during the week prior to necropsy. Animals were housed overnight in metabolic cages.
----Urinalysis Assays: Color, appearance, specific gravity, and urine volume. Semiquantitative analysis: pH, bilirubin, glucose, proteins, ketones, blood, and urobilinogen.
-Anatomic Pathology: A complete necropsy of all animals was performed. Male rats were necropsied on study day 39. Females that delivered were necropsied on ld 5. Female rats that did not deliver were necropsied at least 24 days after the last day of the mating period.
The necropsy included an examination of: the external tissues and all orifices, the cranial, nasal, thoracic and abdominal cavities, and all viscera. Selected tissues of the viscera were incised.
----Examination of uterus: An examination of the uterus for the number of implantation sites was recorded. The uteri of females that did not deliver were stained to determine pregnancy status.
----Organ weights: The following organs were trimmed and weighed: testes,

epididymides, seminal vesicles with coagulating glands (and seminal fluid), prostrate, ovaries, liver, kidneys, adrenals, thymus, spleen, brain, thyroid/parathyroid (after fixation) and heart.
-Histopathology: Histological examinations were conducted on numerous tissues, including tissues exhibiting gross lesions, from all adult rats in the control and high-dose groups, as well as any rats found dead or sacrificed moribund. The histopathological examination of the testes included a qualitative assessment of the stages of spermatogenesis. Microscopic evaluation involved a qualitative assessment of the relationships between spermatogonia, spermatocytes, spermatids and spermatozoa in the seminiferous tubules. Sections of the testes were also examined for the presence of degenerative changes. Also, the liver (males and females), kidneys (males), thyroid glands (males) and gross lesions (males and females) were examined at all dose levels as significant findings were present between the control and high-dose group.

Test substance : IBHK; Lot RA1055T628 (91.2% Purity)
Conclusion : A no-observed effect level (NOEL) for general toxicity could not be determined for male rats, while the NOAEL for general toxicity in females was 100 mg/kg/day. The NOEL for reproductive effects was 300 mg/kg/day. The NOEL for neurological effects was 1000 mg/kg/day, the highest dose level tested.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
02.12.2005 (1)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : other
Route of admin. : gavage
Exposure period : gestation day 6-20
Frequency of treatm. : daily
Duration of test : Up to gd 20
Doses : 250, 500, 750 or 1000 mg/kg/day
Control group : yes
NOAEL maternal tox. : = 250
other: NOEL : = 1000
Embryo/fetal Toxicity
Method : other
Year : 2002
GLP : yes
Test substance : other TS

Method : Probe study based on EPA OPPTS 370.3700, Prenatal Developmental Toxicity Study.
Remark : STATISTICAL ANALYSIS: Maternal body weights, body weight gains, organ weights and feed consumption were evaluated by Bartlett's test for equality of variances. Based on the results, a parametric or nonparametric analysis of variance (ANVOA) was performed. If the ANOVA was significant at alpha=0.05, analysis by Dunnett's Test or the Wilcoxon Rank Sum Test with Bonferroni's correction was performed.
Frequency of pre-implantation loss, post-implantation loss, resorptions per litter and resorptions per fetal population were analyzed using a Censored Wilcoxon Test with Bonferroni's correction. The number of corpora lutea and implantations, and litter size were evaluated using a nonparametric ANOVA followed by the Wilcoxon Rank-Sum Test with Bonferroni's correction. Pregnancy rates were analyzed using the Fisher exact probability Test with Bonferroni's correction. Non-pregnant females, females with resorptions only, or females found to be pregnant after

staining of their uteri were excluded from the appropriate analyses. Statistical outliers were identified using a sequential method and excluded if justified by sound reason.

Result : ANALYTICAL ANALYSIS

-Concentrations: Analyses of the dosing concentrations from the initial preparation indicated mean concentrations of IBHK ranging from 101-102% of the targeted concentrations.
-Stability: Stability analysis of the sample dose suspensions taken 7, 14, and 28 days after preparation revealed mean concentrations that ranged from 94.1-99.2% of the target IBHK concentration.
-Homogeneity: Analysis of multiple samples removed from the low and high dose groups at various levels within the storage vessel confirmed that IBHK was homogenously distributed throughout the dose suspension.

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
-Mortality and day of death: none

-In-Life Observations: Oral administration of IBHK resulted in increased salivation at all dose levels. Increased salivation was observed in all animals (8/8 each) in the 500-1000 mg/kg/day doses, whereas only 5 of 8 animals in the 250 mg/kg/day group exhibited this sign. Salivation was transient, usually ending within one hour of dosing, suggesting a local response to the taste of the test material.

One dam delivered early in the 250 mg/kg/day dose group.

Other clinical signs included a palpable mass on a dam in the 250 mg/kg/day dose level, which was identified as a firm mass-nodule on the left side of the neck at necropsy. Perineal urine soiling was noted in one animal in the 500 mg IBHK/kg/day group on gd 20 and a dam in the 750 mg/kg/day was observed with red vulvular discharge on gd 18. As these signs appeared as isolated incidences, they were not attributed to IBHK treatment.

-Body weight/body weight gain: Exposure to 750 or 1000 mg IBHK/kg/day resulted in a decrease in body weight gains, 10 and 11% respectively, although this decrease was not significant.

Exp. Conc.		BW gain (g) on GD 0-6	6-9	9-12	12-15	15-18	18-21	6-21	0-21
0	Mean	31.0	14.6	19.2	21.8	39.3	36.4	131.3	162.2
	S. D.	5.3	5.5	6.0	5.3	9.2	6.9	17.5	16.1
	N	8	8	8	8	8	8	8	8
250	Mean	36.1	18.6	19.1	21.5	40.4	39.0	140.3	177.9
	S. D.	6.0	4.1	4.0	3.4	7.7	7.9	15.1	16.6
	N	8	8	8	8	8	7	7	7
500	Mean	30.6	12.2	20.2	17.5	37.7	39.2	125.8	156.5
	S. D.	7.2	4.2	3.0	2.6	6.0	7.9	11.5	15.6
	N	8	8	8	8	8	8	8	8
750	Mean	35.3	13.1	20.4	16.7	36.1	32.0	118.2	153.5
	S. D.	7.3	5.3	3.1	3.3	6.3	12.8	19.4	20.5
	N	7	7	7	7	7	7	7	7
1000	Mean	31.8	10.6	19.1	19.8	32.9	34.5	116.9	148.7
	S. D.	7.5	2.3	3.5	4.4	5.7	6.7	14.4	17.9
	N	8	8	8	8	8	8	8	8

-Feed Consumption: There were no significant differences in feed consumption between control and test animals.

Anatomic Pathology

-Organ Weights: Doses of 750 and 1000 mg IBHK/kg/day produced statistically significant increases in absolute (28 and 33%) and relative liver weights (30 and 33%). Relative liver weight was also significantly increased at 500 mg/kg/day (16%). There was a 14% increase in absolute liver weight at 500 mg/kg/day that was considered treatment-related, but not statistically significant. Mean relative kidney weight was significantly increased by 19% and absolute kidney weight was increased by 15%, not statistically significant, at the 1000 mg/kg/day dose level.

Dose (mg/kg/day)		Final Body Weight (g)	Kidneys (g)	Kidneys (g/100)	Liver (g)	Liver (g/100)
0	Mean	390.2	1.867	0.479	14.540	3.717
	S. D.	27.3	0.195	0.043	1.959	0.323
	N=	8	8	8	8	8
250	Mean	405.4	2.050	0.497	15.190	3.777
	S. D.	24.2	0.209	0.023	1.950	0.431
	N=	7a	8	7a	8	7a
500	Mean	384.4	2.006	0.522	16.633	4.329*
	S. D.	14.7	0.194	0.045	1.290	0.315
	N=	8	8	8	8	8
750	Mean	383.4	2.061	0.536	18.583*	4.842*
	S. D.	26.0	0.330	0.063	2.055	0.360
	N=	8	8	8	8	8
1000	Mean	376.2	2.143	0.571*	19.320*	5.140*
	S. D.	18.9	0.206	0.064	1.069	0.241
	N=	8	8	8	8	8

a = varying (N) values due to the exclusion of the final body weight for the animal that delivered early.
* alpha=0.05, statistically different from the control mean by Dunnett's Test.

-Gross Pathology: There were no treatment-related gross pathologic observations.

-Reproductive Parameters: There were no significant treatment-related effects on pregnancy rates, number of corpora lutea, implantations, resorptions per litter with resorptions, or litter size. Mean percent post-implantation loss was significantly increased at 1000 mg/kg/day. An increase in the number of resorptions per litter was observed in the 1000 mg/kg/day dose, but the increase was not statistically significant and there was not a related decrease in the number of viable fetuses as compared to control. A significant decrease in mean percentage pre-implantation loss was seen at 1000 mg/kg/day, but a decrease in this parameter is not considered adverse.

Dose (mg/kg/day)	0	250	500	750	1000
Number Bred	8	8	8	8	8
# Pregnant	8/8	8/8	8/8	7/8	8/8
# Deaths	0	0	0	0	0
# Moribund	0	0	0	0	0
# Aborted	0	0	0	0	0
# Delivered Early	0	1	0	0	0
Pregnancies Detected					

By Stain		NA	NA	NA	1	NA
# Total Litters Resorbed		0	0	0	0	0
# Litters with Viable Fetuses		8	8	8	7	8
# Corpora Lutea per Dam	(Mean)	13.6	14.4	13.1	13.3	13.3
	(S. D.)	1.8	1.9	2.8	3.1	1.4
# Implantations per Dam	(Mean)	11.9	13.6	12.5	12.0	13.0
	(S. D.)	1.1	2.3	2.4	3.2	1.2
Mean % Pre-Implantation Loss	(Mean)	11.98	6.04	4.20	10.56	1.73*
	(S. D.)	10.25	7.00	6.21	16.84	3.20
# Resorptions per Litter	(Mean)	0.4	0.4	0.3	0.4	1.3
	(S. D.)	1.1	0.5	0.5	0.5	1.0
Resorptions/ Litters with Resorptions		3.00 (3/1)	1.00 (3/3)	1.00 (2/2)	1.00 (3/3)	1.67 (10/6)
Mean % Post-Implantation Loss	(Mean)	3.13	2.84	2.03	4.63	9.27*
	(S. D.)	8.84	4.10	3.89	6.52	7.12
Viable Fetuses per Litter	(Mean)	11.5	13.3	12.3	11.6	11.8
	(S. D.)	1.5	2.3	2.4	3.4	0.9

* alpha=0.05, Statistically different from control mean by Wilcox's Test.

Test condition : TEST ORGANISMS
-Sexually mature adult female CD rats
-Age: 10-11 weeks of age
-Weight at study initiation: 200-250g
-Number of animals: 40 time-mated females (8/group)
ADMINISTRATION/EXPOSURE
-Route: oral/gavage
-Doses: The target doses were 0, 250, 500, 750 and 1000 mg IBHK/kg/day. IBHK was administered in a 0.5% METHOCEL suspension and samples were analyzed to confirm concentration verification, stability and homogeneity.
-Exposures: Dams were dosed by gavage daily from gestation day (gd) 6-20.
PARAMETERS ASSESSED DURING STUDY:
-Clinical observations performed and frequency: Clinical observations were conducted daily throughout the study period.
-Body weight/body weight gain: Maternal body weights were recorded on GD 0 (at the supplier), 3, 6, 9, 12, 15, 18 and 21.
-Food consumption: Food consumption was recorded on GD 3-6, 6-9, 9-12, 12-15, 15-18 and 18-21.
-Maternal Necropsy: All animals were submitted for a complete necropsy on gd 21. The eyes were examined by visual inspection. Weights of the liver and kidneys were recorded and organ to body ratios calculated. Sections of liver, kidneys and gross lesions were preserved.
-Examination of uterus: An examination of the uterus for the number of implantation sites and resorptions, and the ovaries for the number corpora lutea was performed. The position and number of early and/or late resorptions and normally developing fetuses were recorded. Corpora lutea for non-pregnant animals were not counted. The uteri of animals lacking

visual implantations were stained and examined for evidence of early resorptions to verify pregnancy status.

Test substance	:	IBHK; Lot No. 1229 (91.3% Purity)
Conclusion	:	The no-observed-adverse-effect level (NOAEL) for maternal toxicity was 250 mg/kg/day while 1000 mg/kg/day was considered a no-observed-effect-level (NOEL) for embryo/fetal toxicity.
Reliability	:	(1) valid without restriction

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Species	:	rat
Sex	:	female
Strain	:	other:CD
Route of admin.	:	gavage
Exposure period	:	See Section 5.8.1
Frequency of treatm.	:	See Section 5.8.1
Duration of test	:	See Section 5.8.1
Doses	:	100, 300, 1000 mg IBHK/kg/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 100 mg/kg bw
other: NOEL	:	= 300 - mg/kg bw
Embryo/fetal Toxicity		
Method	:	other: OECD 422 and US EPA OPPTS 870.3650
Year	:	2005
GLP	:	yes
Test substance	:	other TS

Method	:	See Section 5.8.1
Result	:	See Section 5.8.1
Test substance	:	IBHK; lot RA1055T628 (91.2% Purity)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

02.12.2005 (1)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT